Pediatrics and Neonatology (2016) 57, 195–200

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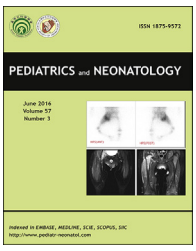

ORIGINAL ARTICLE

Decreased Cystatin C–Estimated Glomerular Filtration Rate Is Correlated with Prolonged Hospital Stay in Transient Tachypnea of Newborn Infants

Bo Bae Kim [a], Sung-Hoon Chung [a], Hoi-Soo Yoon [a], Won-Ho Hahn [b], Chong-Woo Bae [a], Yong-Sung Choi [a,*]

[a] *Department of Pediatrics, Kyung Hee University School of Medicine, Seoul, South Korea*
[b] *Department of Pediatrics, School of Medicine, Seoul Hospital, Soon Chun Hyang University, Seoul, South Korea*

Received Mar 4, 2015; received in revised form Jun 4, 2015; accepted Aug 3, 2015
Available online 3 October 2015

Key Words
transient tachypnea of the newborn;
glomerular filtration rate;
cystatin C

Background: Transient tachypnea of the newborn (TTN) is a benign disorder with a variable clinical course that often leads to hospitalization. The aim of this study was to assess and validate the relationship between the serum cystatin C level and symptom duration in infants with TTN.
Methods: Forty newborns presenting with TTN and who had undergone serum cystatin C (Cys C) tests on the first day of admission to the Kyung Hee University Hospital (Seoul, Korea) from 2009 to 2013 were included. The serum Cys C level, creatinine (Cr) level, estimated glomerular filtration rate (eGFR), and tachypnea duration were correlated retrospectively.
Results: The median gestation period was 37.8 ± 3.8 weeks and the mean birth weight was 3.2 ± 0.4 kg. Tachypnea duration was 3.3 ± 2.0 days. Serum Cys C and Cr levels were 1.7 ± 0.2 mg/L and 0.8 ± 1.2 mg/dL, respectively. Tachypnea duration was significantly positively correlated with the serum levels of Cys C and significantly negatively correlated with Cys C-based eGFR ($p = 0.016$), but was not significantly correlated with the serum Cr level or Cr-based eGFR. When tachypnea duration was compared between infants with Cys C level <1.6 mg/L ($n = 15$; Group A) and infants with Cys C level ≥ 1.6 mg/L ($n = 25$; Group B), the symptom duration was significantly shorter in Group A infants ($p = 0.011$).
Conclusion: Tachypnea duration was shorter with higher Cys C-based eGFR in infants with TTN.

* Corresponding author. Department of Pediatrics, Kyung Hee University Hospital, 23 Kyungheedae-ro, Dongdaemun-gu, Seoul, zip code: 130-872, South Korea.
E-mail address: feelhope@khu.ac.kr (Y.-S. Choi).

http://dx.doi.org/10.1016/j.pedneo.2015.08.006

1. Introduction

Transient tachypnea of the newborn (TTN), a clinical syndrome first described by Avery et al[1] in 1966, is accompanied by respiratory distress. Its pathogenesis is unclear, although it has been suggested that the development of TTN may be associated with a delay in the reabsorption of pulmonary alveolar fluid that prevents lung collapse during the fetal period.[1,2] Most cases of TTN consist of benign self-limiting pulmonary disease, except for occasional severe cases that require laboratory tests, chest radiography, and admission into the neonatal intensive care unit (NICU) for intensive respiratory treatment. The incidence of TTN is ~1–2% in all neonates,[3] and the average symptom duration is 2–5 days.[4]

Despite the relatively short hospital stay and benign course, TTN is associated with social and financial burdens because the affected infants are usually admitted to NICUs.[5] Therefore, several studies pertaining to TTN symptom duration have been published. These studies have focused on fluid redistribution because some clinicians have used loop diuretics to treat patients with TTN. A recent study revealed no apparent advantage in using furosemide,[6] although another study demonstrated a significant improvement in fluid-restricted TTN infants, which implicates an association between fluid balance and TTN symptoms.[7]

Because of its active effects on body fluid balance, the renal function of infants with TTN was analyzed in the current study to test the hypothesis that infants with a shorter symptom duration would have better renal function. Serum cystatin C (Cys C) and creatinine (Cr) were chosen for calculating the estimated glomerular filtration rate (eGFR) because they are representative markers of renal function.[8] The aim of the current study was to evaluate the relationship between the eGFR, using serum Cys C, and symptom duration in infants with TTN.

2. Patients and methods

2.1. Participants

This retrospective study was conducted at a single tertiary care center—Kyung Hee University Hospital (Seoul, Korea)—and was based on medical chart reviews. Before the data were reviewed and analyzed, the Institutional Review Board of the Kyung Hee University Hospital approved the present study. Patients admitted to the NICU of the Kyung Hee University Hospital from January 2009 to July 2013 were screened with the following inclusion criteria: gestational age $\geq$37 weeks; birth weight $\geq$2500 g; a diagnosis of TTN without hyaline membrane disease, pneumonia, or pneumothorax, as confirmed through chest radiograph; and serum Cys C and Cr levels that were measured on the 1st day of admission. Infants were excluded that had renal failure (i.e., sustained plasma creatinine level $\geq$ 1.5 mg/dL)[9] or oliguria (i.e., urine flow $<$ 1 mL/kg/h).[10] The Cys C level at the time of admission was not assessed because of renal impairment but as part of a routine serum chemistry battery.

2.2. Data collection

Individual medical records were transcribed into the case report forms and included sex, gestational age, and birth weight. Data pertaining to Apgar scores at 1 minute and 5 minutes, type of delivery, urine output, serum Cys C level on the 1st day of admission, and serum Cr were also collected. Mean urine output values measured every 1–3 hours during the admission period were used as a representative value of urine output. Serum levels of Cys C and Cr were measured by an automated chemical analyzer (Toshiba, Nasushiobara, Japan) using HiSens Cys-C LTIA (HBi Co., Ltd., Anyang, Korea) and serum Cr (Kanto Chemical Co., Tokyo, Japan), respectively. Serum Cr-based eGFR (Cr-eGFR) and serum Cys C-based eGFR (Cys-eGFR) were calculated using the following equations: (1) Cr-eGFR (in term neonates) = 0.45 $\times$ length (cm)/serum Cr (mg/dL) and (2) Cys C-eGFR = 137/Cys C − 20.4 (Bokencamp A).[11] Based on the Cys C values, a cutoff of 1.6 mg/L (corresponding to Cys C-eGFR 65 mL/min/1.73 m^2) was used to classify patients into two subgroups: (1) the low Cys C group (Group A; n = 15, Cys C $<$ 1.6 mg/L, and Cys C-eGFR $>$ 65 mL/min/1.73 m^2) and (2) the high Cys C group (Group B; n = 25, Cys C $\geq$ 1.6 mg/L, and Cys C-eGFR $\leq$ 65 mL/min/1.73 m^2).

2.3. Definitions

The time after admission to the resolution of tachypnea was recorded. The measured respiratory rates (RRs) were also reviewed from medical charts. Tachypnea was defined as a breath rate of more than 60 breaths/min. The RR was represented by the mean value of the RRs measured every 1–3 hours during the admission period of the patient. We assessed the average values of every 8-hour period. Resolution of tachypnea was defined as the day when the 8-hour period average RR was below 60 breaths/min in two or more consecutive periods.

2.4. Statistical analysis

The relationships between TTN symptom duration, serum Cys C level, serum Cr level, and eGFRs measured on hospital Day 1 were analyzed. The type of delivery, Apgar scores at 1 minute and 5 minutes, and average gestational period were also analyzed. All statistical analyses were conducted using SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA). The data are expressed as the mean $\pm$ the standard deviation. The Mann–Whitney U test was used to evaluate the differences between the low and high Cys C subgroups. Pearson's correlations and multivariate regression analyses were performed to examine the relationships between symptom duration, urine output, Cr, cystatin C, Cr-eGFR, and Cys C-eGFR. Statistical significance was set at $p < 0.05$.

3. Results

From January 2009 to July 2013, a total of 65 TTN patients older than 37 gestational weeks with a birth weight $>$2500 g

were admitted to the NICU of Kyung Hee University Hospital. Forty patients who met all inclusion criteria were included as participants.

3.1. Baseline characteristics

The patient characteristics are presented in Table 1 and expressed as the median and range.

3.2. Correlations with symptom duration

Symptom duration, urine output, serum Cys C, serum Cr, Cys C-eGFR, and Cr-eGFR were correlated. No significant correlations existed between TTN symptom duration and the following: urine output, serum Cr, and Cr-eGFR ($p = 0.336$, $p = 0.653$, and $p = 0.889$, respectively). However, serum Cys C and TTN symptom duration were positively correlated ($R = 0.378$, $p = 0.016$), while Cys C-eGFR was negatively correlated ($R = -0.778$, $p = 0.016$; Table 2). Simple linear regression analysis showed a significant association between Cys C and symptom duration ($R^2 = 0.157$, $p = 0.015$; Figure 1). Multivariate regression analysis conducted to adjust for gestational age, birth weight, sex, Apgar scores, delivery type, and urine output demonstrated that the aforementioned results remained statistically significant ($R^2 = 0.141$, $p = 0.02$).

3.3. Correlations with urine output

Urine output was correlated with serum Cr, Cr-eGFR, serum Cys C, and Cys C-eGFR. Urine output was not significantly correlated with serum Cr or Cr-eGFR ($p = 0.677$ and $p = 0.359$, respectively). However, serum Cys C and urine output showed a significantly negative correlation, ($R = -0.398$, $p = 0.011$). By contrast, Cys C-eGFR showed a significantly positive correlation with urine output, ($R = 0.363$, $p = 0.021$; Table 2).

3.4. Differences between the high eGFR group and low eGFR group

Symptom duration was shorter in Group A (median, 1.44 days) than in Group B (median, 2.28 days, $p = 0.011$), and urine output was greater in Group A (median, 81.8 mL/kg/d) than in Group B (median, 55.6 mL/kg/d, $p = 0.01$; Table 1). The cutoff value of 1.6 mg/dL Cys C had a sensitivity of 71.4% and a specificity of 47.4% based on a receiver operating characteristic (ROC) curve analysis.

4. Discussion

The current study demonstrated that the serum Cys C level and the Cys C-eGFR were significantly correlated with TTN symptom duration. The TTN symptom duration was longer in infants with higher serum Cys C levels and lower eGFR levels. The pathogenesis of TTN is unclear, although a delay in the clearance of the fetal lung fluid has been considered as a potential cause.[1] Fetal lung fluid has an important role in fetal lung development through maintaining residual volume to form the fetal lung capacity. Reabsorption of the lung fluid begins 2–3 days before birth, and the epinephrine surge during labor further accelerates this process.[12–14] After the birth of infants with TTN, diuretic treatment has occasionally been used under the assumption that facilitating diuresis would further promote the transportation of lung fluid into the pulmonary vascular bed.[15] However, according to Kassab et al,[16] furosemide treatment in infants with TTN failed to alter the duration of symptoms or the length of their hospital stay. By contrast, Stroupstrup et al[7] showed that fluid restriction reduced the duration of respiratory support and associated hospitalization costs in TTN neonates, which suggests an association between fluid status and TTN symptoms.

The relationship between renal function and symptom duration in TTN infants remains controversial. The results

Table 1 The characteristics of newborn infants with transient tachypnea of the newborn. The infants are divided into two groups: Group A (i.e., Cys C $<$ 1.6 mg/L) and Group B (i.e., Cys C $\geq$ 1.6 mg/L).

N	Total	Group A	Group B	*p*
	40	15	25	N/A
Gestational age (wk)	38.1 (35.0–41.7)	38.7 (35.0–41.7)	38.0 (35.9–41.7)	0.288
Birth weight (kg)	3223 (2420–4050)	3310 (2600–3961)	3200 (2420–4050)	0.675
Apgar score	8 (5–10)/9 (8–10)	8 (5–9)/9 (8–10)	8 (6–10)/9 (8–10)	0.466/0.314
C-section	25 (62.5)	6 (40)	8 (32)	0.354†
Urine output (mL/kg/d)	66.5 (3.3–127.3)	81.8 (59.2–109.2)	55.6 (3.3–127.3)	0.010*
Serum cystatin C (mg/dL)	1.65 (1.1–2.2)	1.5 (1.1–1.5)	1.8 (1.6–2.2)	0.000*
eGFR-Cys (mL/min/1.73m^2)	62.7 (41.9–104.1)	70.9 (70.9–104.1)	55.7 (41.9–65.2)	0.000*
Serum creatinine (mg/dL)	0.6 (0.3–8)	0.6 (0.3–8)	0.7 (0.4–0.9)	0.150
eGFR-Cr (mL/min/1.73m^2)	35.0 (2.1–79.5)	36.8 (2.1–79.5)	34.1 (25.0–58.5)	0.304
Symptom duration (d)	1.70 (0.05–8.03)	1.44 (0.05–3.41)	2.28 (0.43–8.03)	0.011*
Oxygen duration (d)	1.70 (0–7.49)	1.10 (0–3.86)	2.34 (0.01–7.49)	0.148

Data are presented as n (%) or median (range). Subgroup analysis between Group A and Group B was performed by the Mann–Whitney *U* test.

C-section, caesarean section; Cr, serum creatinine; Cys, cystatin C, eGFR, estimated glomerular filtration rate.

* Indicates a significant difference at $p < 0.05$.

† The Chi square test was performed.

Table 2 The correlations between symptom duration in infants with tachypnea of the newborn and renal parameters.

	Symptom duration (d)		Cystatin C (mg/dL)		Creatinine (mg/dL)		Urine output (cc/kg/d)		eGFR-Cr (mL/min/1.73m^2)		eGFR-Cys (mL/min/1.73m^2)	
	R	*p*	R	*p*	R	*p*	R	*p*	R	*p*	R	*p*
Symptom duration	—	—	0.378	0.016*	−0.078	0.653	−0.156	0.336	0.024	0.889	−0.378	0.016*
Cystatin C	0.378	0.016*	—	—	−0.199	0.243	−0.398	0.011*	−0.252	0.138	−0.979	0.000*
Creatinine	−0.078	0.653	−0.199	0.243	—	—	−0.072	0.677	−0.535	0.001*	0.220	0.196
Urine output	−0.156	0.336	−0.398	0.011*	−0.072	0.677	—	—	0.157	0.359	0.363	0.021*
eGFR-Cr	0.024	0.889	−0.252	0.138	−0.535	0.001	0.157	0.359	—	—	0.275	0.104
eGFR-Cys	−0.378	0.016*	0.979	0.000*	0.220	0.196	0.363	0.021*	0.275	0.104	—	—

Cr, serum creatinine; Cys, cystatin C; eGFR, estimated glomerular filtration rate; R, Pearson's correlation coefficient.
* Indicates a statistical significance at $p < 0.05$.

of the current study demonstrated a significant association between symptom duration and Cys C, but not with urine output. This suggests that the degree of maturation such as managing ions through channels, as opposed to simple urine output, is a more important factor for consideration. A commonly shared linkage between the lungs and kidneys in neonates immediately after birth remains speculative. Although we did not examine specific ion channel mechanisms in the current study, we suggest that epithelial sodium channels (ENaCs) and sodium-potassium adenine triphosphatase (Na/K-ATPase) may be key mechanisms in this linkage, based on their important roles in fluid management in the lungs and in the kidneys. During the dynamic process of the fluid status change in the lungs in the peripartum stage, sodium (Na^+) is the most important actively transported ion.[17] Epithelial sodium channels allows Na^+ to move from the alveolar lumen through the basolateral membrane, and Na/K-ATPase relocates Na^+ to the interstitium.[12] Shortly after the labor process is induced, the expression of ENaC and Na/K-ATPase in the lung epithelium accelerates, which changes the lung epithelium from a chloride-secreting membrane to a sodium-absorbing membrane. These changes facilitate the absorption of lung fluid into the pulmonary vascular bed and into the interstitium.[18–20]

Infants presenting with TTN have ineffective ion channel switching in the pulmonary epithelium,[7] whereas other mechanical factors also affect the onset of TTN.[4] A similar process has also been demonstrated in the kidneys where Na^+ transport has an important role in the antenatal maturation of the kidneys. The highly maintained fractional excretion of Na^+ decreases dramatically at the beginning of

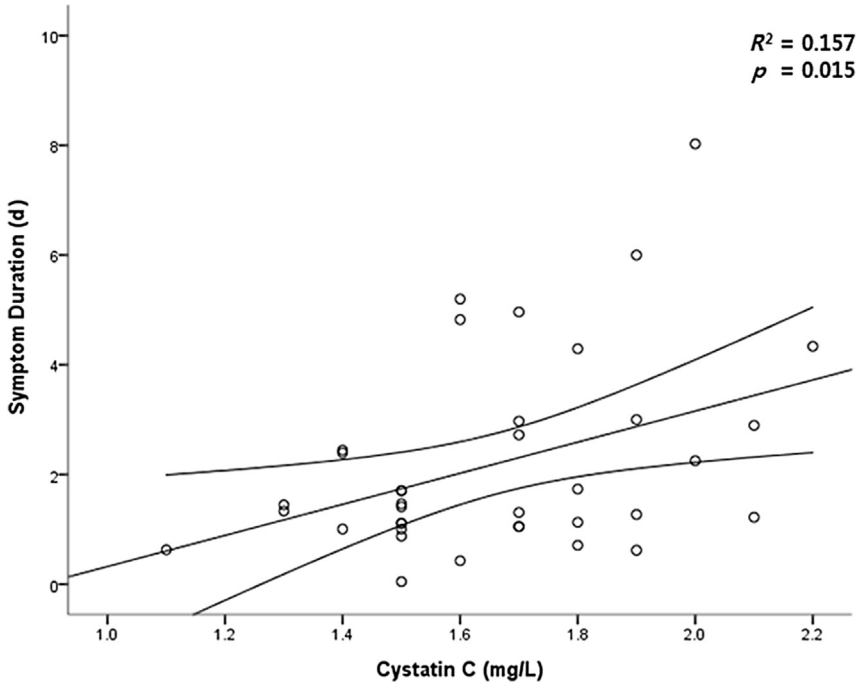

Figure 1 Tachypnea duration, based on the serum cystatin C level. A positive correlation between symptom duration and serum Cys C level ($p = 0.016$) is evident. The solid lines represent the regression line and mean confidence interval. The formula used for linear regression analysis is as follows: tachypnea duration (days) = 2.835 × serum Cystatin C (mg/dL) − 2.512.

birth,[21,22] and results in the removal of interstitial fluid. The transition from a negative to a positive Na^+ balance subsequently occurs.[23] Epithelial sodium channel in the distal convoluted tubule, collecting tubule, and principal cells of the collecting duct also have important roles in Na^+ reabsorption, and collectively regulate the extracellular fluid volume in a precise manner. The finding that the α subunit of Na/K-ATPase and the nephrons have parallel maturation also supports such an association.[24] Thus, ENaC and Na/K-ATPase determine the fluid volume in the lungs and in the kidneys. These similar mechanisms, which are associated with fluid reabsorption, suggest a connection between renal function and TTN.[25]

There are several risk factors that aggravate TTN symptoms such as male sex, Cesarean section delivery, low Apgar score, acidosis, and myocardial dysfunction.[26,27] Lactate dehydrogenase and digoxin-like immunoreactive substance have also been implicated in a few studies.[28,29] However, practical biochemical markers that can be used to predict the prognosis of TTN have yet to be discovered. In the current study, serum GFR and Cys C were used as biomarkers to estimate the glomerular filtration rate (GFR) in infants with TTN. The Cys C level is especially useful in neonates, and unlike serum Cr, it is unaffected by gestational age or maternal GFR.[7,30,31] Although controversy remains, the normal physiologic ranges of Cys C and Cys C-eGFR in term neonates (i.e., gestational period $>$ 37 weeks) in the first 3 days after birth are 1.21 $\pm$ 0.31 mg/L and 65.55 $\pm$ 30.45 mL/min/1.73 m^2, respectively.[26] Based on our eGFR equation, which differed from the equations used in the aforementioned studies, the eGFR of 65 mL/min/1.73 m^2 in infants with TTN was associated with a Cys C level of 1.6 mg/dL. The corresponding eGFR value for Cys C 1.6 mg/dL was 65.225 mL/min/1.73 m^2 when using our formula. In addition, 1.6 mg/dL of Cys C corresponded to our observed median level of Cys C in all 40 patients examined. Based on the cutoff Cys C level of 1.6 mg/dL, infants with a higher Cys C and lower a Cys C-eGFR had a longer tachypnea duration. The ROC curve using this cutoff value demonstrated a sensitivity of 71.4% and a specificity of 47.4%. These results suggest that this method may not be an excellent test tool, but is more likely a useful indicator, if further study is warranted.

To the best of our knowledge, this is the first attempt to evaluate the relationships between Cys C, eGFR calculated using Cys C, and TTN symptom duration. Serum Cys C and Cys C-eGFR showed significant correlations with TTN symptom duration, which suggests an association between renal function and TTN symptom duration. In a different study by Kara et al,[10] the authors hypothesized that insufficient lung fluid elimination resulted from a lack of N-terminal probrain natriuretic peptide (NT-proBNP) in infants with TTN. However, no significant difference was found between the NT-proBNP levels in infants with TTN and members of a control group.[10]

The principal limitation of the current study was the inability to exclude other factors such as sepsis or hyperthyroidism that can affect serum Cys C levels. In addition, the small number of patients in our cohort limited the statistical power of the study. Because of the low R^2 in our study, careful deliberation and further studies will be required.

Data from the current study revealed that serum Cys C and serum Cys C-eGFR showed positive and negative correlations with TTN symptom duration, respectively. The high GFR group showed a statistically shorter TTN symptom duration as compared with the low GFR group. However, Cr-eGFR and urine output did not correlate with TTN symptom duration. Further studies regarding the utilization of Cys C as a cost efficient and easily obtained predictive index for TTN symptom duration are needed. Moreover, treatments for TTN that take measurements of renal function into account will also require additional research.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

References

1. Avery ME, Gatewood OB, Brumley G. Transient tachypnea of newborn. Possible delayed resorption of fluid at birth. *Am J Dis Child* 1966;**111**:380—5.
2. Rimmer S, Fawcitt J. Delayed clearance of pulmonary fluid in the neonate. *Arch Dis Child* 1982;**57**:63—7.
3. Ramachandrappa A, Jain L. Elective cesarean section: its impact on neonatal respiratory outcome. *Clin Perinatol* 2008;**35**:373—93.
4. Bak SY, Shin YH, Jeon JH, Park KH, Kang JH, Cha DH, et al. Prognostic factors for treatment outcomes in transient tachypnea of the newborn. *Pediatr Int* 2012;**54**:875—80.
5. Consortium on Safe Labor, Hibbard JU, Wilkins I, Sun L, Gregory K, Haberman S, et al. Respiratory morbidity in late preterm births. *JAMA* 2010;**304**:419—25.
6. Karabayir N, Kavuncuoglu S. Intravenous frusemide for transient tachypnoea of the newborn: a randomised controlled trial. *J Paediatr Child Health* 2006;**42**:640—2.
7. Stroustrup A, Trasande L, Holzman IR. Randomized controlled trial of restrictive fluid management in transient tachypnea of the newborn. *J Pediatr* 2012;**160**:38—43.
8. Andersen TB. Estimating renal function in children: a new GFR-model based on serum cystatin C and body cell mass. *Dan Med J* 2012;**59**:B4486.
9. Chevalier RL, Campbell F, Brenbridge AN. Prognostic factors in neonatal acute renal failure. *Pediatrics* 1984;**74**:265—72.
10. Kara S, Tonbul A, Karabel M, Akca H, Uras N, Tatli M. The role of serum N-terminal pro-brain natriuretic peptide in transient tachypnea of the newborn. *Eur Rev Med Parmacol Sci* 2013;**17**:1824—9.
11. Zappitelli M, Parvex P, Joseph L, Paradis G, Grey V, Lau S, et al. Derivation and validation of cystatin C-based prediction equations for GFR in children. *Am J Kidney Dis* 2006;**48**:221—30.
12. Polin RA, Fox WW, Abman SH. *Fetal and neonatal physiology*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2011. p. 907—12.
13. Walters DV, Olver RE. The role of catecholamines in lung liquid absorption at birth. *Pediatr Res* 1978;**12**:239—42.
14. Brown MJ, Olver RE, Ramsden CA, Strang LB, Walters DV. Effects of adrenaline and of spontaneous labour on the secretion and absorption of lung liquid in the fetal lamb. *J Physiol* 1983;**344**:137—52.
15. Wickerts CJ, Berg B, Frostell C, Schmidt J, Blomqvist H, Rösblad PG, et al. Influence of hypertonic-hyperoncotic solution and furosemide on canine hydrostatic pulmonary oedema resorption. *J Physiol* 1992;**458**:425—38.

16. Kassab M, Khriesat WM, Bawadi H, Anabrees J. Furosemide for transient tachypnoea of the newborn. *Cochrane Database Syst Rev* 2013;**6**:CD003064.
17. Olver RE, Ramsden CA, Strang LB, Walters DV. The role of amiloride-blockable sodium transport in adrenaline-induced lung liquid reabsorption in the fetal lamb. *J Physiol* 1986; **376**:321—40.
18. Barker PM, Olver RE. Invited review: Clearance of lung fluid during the perinatal period. *J Appl Physiol (1985)* 2002;**93**: 1542—8.
19. Smith DE, Otulakowski G, Yeger H, Post M, Cutz E, O'Bordovich HM. Epithelial Na(+) channel (ENaC) expression in the developing normal and abnormal human perinatal lung. *Am J Respir Crit Care Med* 2000;**161**:1322—31.
20. Taylor PM, Allen AC, Stinson DA. Benign unexplained respiratory distress of the newborn infant. *Pediatr Clin North Am* 1971;**18**:975—1004.
21. Bueva A, Guignard JP. Renal function in preterm neonates. *Pediatr Res* 1994;**36**:572—7.
22. Al-Dahhan J, Haycock GB, Chantler C, Stimmler L. Sodium homeostasis in term and preterm neonates. I. Renal aspects. *Arch Dis Child* 1983;**58**:335—42.
23. Al-Dahhan J, Haycock GB, Nichol B, Chantler C, Stimmler L. Sodium homeostasis in term and preterm neonates. III. Effect of salt supplementation. *Arch Dis Child* 1984;**59**: 945—50.
24. Minuth WW, Gross P, Gilbert P, Kashgarian M. Expression of the alpha-subunit of Na/K-ATPase in renal collecting duct epithelium during development. *Kidney Int* 1987;**31**:1104—12.
25. Kashlan OB, Kleyman TR. Epithelial Na(+) channel regulation by cytoplasmic and extracellular factors. *Exp Cell Res* 2012; **318**:1011—9.
26. Tudehope DI, Smyth MH. Is "transient tachypnoea of the newborn" always a benign disease? Report of 6 babies requiring mechanical ventilation. *Aust Paediatr J* 1979;**15**:160—5.
27. Halliday HL, McClure G, Reid MM. Transient tachypnoea of the newborn: two distinct clinical entities? *Arch Dis Child* 1981;**56**: 322—5.
28. Ozkiraz S, Gokmen Z, Boke SB, Kilicdag H, Ozel D, Sert A. Lactate and lactate dehydrogenase in predicting the severity of transient tachypnea of the newborn. *J Maternal Fetal Neonatal Med* 2013;**26**:1245—8.
29. Yalaz M, Levent E, Olukman M, Calkavur S, Akisu M, Kultursay N. Role of digoxin-like immunoreactive substance in the pathogenesis of transient tachypnea of newborn. *Biomed Res Int* 2013;**2013**:704763.
30. Dorum S, Silfeler I, Dorum BA, Silfeler DB, Canbak Y, Say A. Reference values of serum cystatin-C for full-term and preterm neonates in Istanbul. *Indian J Pediatr* 2012;**79**:1037—42.
31. Hahn WH, Bae CW. Reference intervals of serum cystatin C/creatinine ratio of 30 postnatal days in neonates. *Pediatr Nephrol* 2014;**29**:311—4.